REMARKS

Reconsideration and withdrawal of any rejection of the application, and allowance of the claims, especially in view of the remarks made herein, are respectfully requested.

Claims 11, 16-20 and 22-26 are pending in this application. Claims 11, 16-20 and 22-26 have been amended; claims 12-15 and 21 have been cancelled. Cancelled claims 12, 13 and 21 were Markush-type claims from which a species election was made. Presently, the elected species of anesthetic is lidocaine and the elected species of analgesic is morphine. The election of species was made with the understanding that the generic claims will be searched once the species is otherwise determined to be patentable. MPEP 803.02. Applicants reserve the right to elect further species for prosecution following allowance of claim 1,10 and 36-60, either in the present application or in divisional application(s).

No new matter is added.

It is submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§101, 102, 103 and 112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments to the claims are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the claim amendments is found throughout the specification.

The Rejection Under 35 U.S.C. § 103 is Overcome

Claims 11-13 and 16-26 were rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Stein (U.S. Patent No. 5,948,389) and Saito *et al.*

The present invention is directed to methods of using topical pharmaceutical compositions, formulated with at least morphine and lidocaine, and to methods of providing pain relief to a subject through topical administration of the composition in an amount and a duration sufficient to potentiate a synergistic antinociceptive response. Topical administration of the pharmaceutical compositions advantageously results in insubstantial, if any, systemic absorption. Presently, the elected species of anesthetic is lidocaine and the elected species of analgesic is morphine. The claims have been amended to reflect the group and species election required by the Office Action.

For an obviousness rejection under § 103 to be proper, both the suggestion of the claimed invention and the expectation of success must be found in the prior art. *In re Dow*, 5 U.S.P.Q.2d

1529, 1531 (Fed. Cir. 1988). The cited references, taken alone or together, fail to provide a suggestion, much less an expectation, of synergistic potentiation between the peripheral pathways that mediate antinociceptive responses.

I. The State of the Art Did Not Recognize the Potential for Antinociceptive Synergism at Peripheral Sites

Prior to the teaching in the instant application, the importance of peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are administered together with local anesthetics was unexpected given the state of the art.

In fact, several medical reports published before the filing of the present application teach that methods comprising the topical use of morphine fail to stimulate peripheral sites (all documents referred to herein are supplied on the Information Disclosure Statement accompanying this response):

For example, Raja *et al.* (Anesthesiology 77:1143-7; 1992) describe a randomized, double-blind study comparing the analgesic efficacy of bupivacaine and morphine administered intraarticularly in 47 patients having undergone arthroscopic knee surgery. The analgesic efficacy of the treatments were determined up to 72 hours following surgery by postoperative pain scores (VAS) and the amount of supplemental opioid required by each patient. A first group of patients received 20 ml of normal saline with 100 μg epinephrine. A second group received 20 ml of 0.25% bupivacaine and 100 μg of epinephrine. A third group received 3 mg of morphine and 100 μg of epinephrine in 20 ml of normal saline (15% morphine). All medicaments were administered by injection into the joint space of the knee via an 18-G needle following arthroscopic surgery. Raja *et al.* did not find any analgesic effect and/or activation of opioid receptors in the periphery as a result of intra-articular morphine administration. For example, the authors state on page 1146 that their study "fails to demonstrate functional opiate receptors in the knee joint in a clinical model of acute injury." Further, the authors conclude on

page 1146 "that no evidence for a peripheral opiate-receptor mediated analgesia could be demonstrated in patients undergoing arthroscopic knee surgery under epidural anesthesia."

Rosenstock *et al.* (Reg. Anesth. 21:93-8; 1996) describe a double-blind, randomized, placebo-controlled study to evaluate the possible immediate and long-term analgesic effect of morphine injected incisionally in patients undergoing minor abdominal surgery (inguinal herniotomy). Following surgery, the patients were divided randomly into one of four groups. The first group received 5 mg of morphine (in 6 ml of saline; 83% w/v) infiltrated in the edges of the surgical wound. The second group received 5 mg of morphine (in 6 ml of saline; 83% w/v) injected in the subcutaneous layer of the surgical wound. The third group received 5 mg of morphine intravenously. The fourth group (placebo) had 6 ml of saline injected in the edges of the surgical wound. Any resulting analgesia was assessed with visual analog scale (VAS) scores over the course of 7 days following the operation. Further, the dosage and frequency of supplemental analgesics (acetaminophen and morphine) required by each patient was considered. However, Rosenstock *et al.* did not find any difference in analgesic effect among the four groups. That is, the placebo group (group 4) provides statistically the same level of analgesia as the three groups having been administered morphine. Similarly, the results did not show any statistical differences between the group in VAS scores nor did the groups show any statistical difference in the postoperative consumption of acetaminophen, alfentanil, or fentanyl. The authors conclude on page 96 that "neither an immediate nor delayed postoperative analgesic effect of incisional morphine could be demonstrated..." in the study.

Picard *et al.* (Pain 72:309-18; 1997) reviewed 26 randomized controlled trials ("RCT") carried out from 1987 through 1996 each directed at understanding whether an analgesic effect could be attained through activation of peripheral opioid receptors. In total, the 26 RCTs studied 925 patients, of which 485 received an opioid, including morphine, fentanyl, alfentanil, buprenorphine and butorphanol. The efficacy of the peripherally-applied analgesics was tested using a variety of surgical methods and analgesic administration methods, including intrapleural, intraperitoneal, incisional, and dental injections, perineural blocks, and brachial plexus sheath injections.

In reviewing the results and conclusions reached by the primary authors of each study to assess the evidence for peripheral opioid analgesia, the current authors conclude in the abstract that none of the studies provided "evidence for a clinically relevant peripheral analgesic efficacy

of opioids in acute pain." Picard *et al.* argue that the results of the 26 RCTs reviewed were either unequivocally negative (i.e., lacking support for peripheral opioid analgesia) or that the results were not clinically relevant. The current authors further state on page 316 that the primary authors "tended to over-interpret their findings and to confuse statistical significance with clinical relevance. Inattentive or uncritical readers [of the studies] may be misled into a false perception of treatment efficacy." Further, the current authors conclude on page 316 that the "clinical use of peripheral opioids requires much more evidence than we have at present."

Yarussi *et al.* (Reg. Anesth. Pain. Med. 24:142-5; 1999) describe a study to evaluate the post-operative analgesic effects, if any, of incisionally-administered morphine in patients undergoing lumpectomies and axillary node dissections in the treatment of breast cancer. The study was carried out in a double-blind, placebo-controlled fashion and involved 45 patients. Prior to surgery, each patient was put under general anesthesia. The patients were then randomized into 3 groups: a first group wherein the surgical site was irrigated for 5 minutes with a 6% solution of morphine sulphate (6 mg in 100 ml of buffer); a second group wherein the 6% solution of morphine sulphate (6 mg in 100 ml of buffer) was administered by intramuscular injection; and a third group wherein the surgical site was irrigated with a placebo (100 ml of buffer) for 5 minutes. Analgesia was assessed by using a visual analog scale card (VAS), supplemental opioid (e.g. fentanyl) consumption, and incidences of side-effects. The authors did not detect any analgesic effect in any morphine-administered group relative to the placebo group. The authors conclude on page 144 that they are "unable to demonstrate any analgesic benefits after topical administration of morphine [at the surgical site]."

II. The Prior Art Teaches Away From Use of Topical Morphine or Lidocaine

Several medical reports published before the filing of the present application teach that use of morphine as a topical composition provides an insufficient effect, a finding that teaches away from the present invention.

Moore *et al.* (Br. J. Clin. Pharmacol. 37:227-30; 1994) describe two consecutive studies on twenty patients to test the possibility of attaining opioid-induced analgesia through the activation of opioid receptors at peripheral sites of molar tooth sockets following the bilateral removal of the third molars. For each patient, the third molars were surgically removed a month apart. After the first surgery, a morphine gel was topically administered to the tooth socket having morphine at a concentration of either 100 ng/ml (0.01% w/v per 300 ul gel volume) or

100 ug/ml (10% w/v per 300 ul gel volume). After the second surgery, a placebo gel was administered to the tooth socket. Administration of the medicaments was carried out in a double-blind fashion. The overall level of analgesia provided by the morphine gel was assessed by patient-administered visual analogue scales (VAS) and by the dosage and frequency of escape analgesia requested by each patient.

The results obtained do not show an antinociceptive response at peripheral sites following topical administration of morphine in the tooth socket. For example, on page 228 of Moore *et al.*, the authors indicate that there is "no significant difference...between both locally applied morphine treatments and placebo." In other words, the data did not demonstrate any analgesic effect upon topical administration of morphine at the periphery (tooth socket) over and above the effect provided by the placebo.

The authors further state that the results show "no clear efficacy in the control of postoperative pain after third molar surgery. Any 'peripheral activity' that morphine may exhibit does not thus appear to result in any antinociceptive effect..." The authors conclude that that no antinociceptive response to topical morphine administration is achieved at peripheral sites. Moore et al. teaches away from a topical, antinociceptive composition comprising morphine and therefore, from the present invention.

Roy and Flyn (Pharm. Research. 6:825-832; 1989) describe a study comparing absorption properties of six narcotic compounds and/or analgesics, including morphine. In this study, absorption is assessed by measuring the permeability coefficients of each drug on skin derived from human cadavers. Both acidic and free base forms of the drugs are tested. The study was carried out by obtaining skin from 48-hour human cadavers, which was then subjected to a skin permeation assay to test whether the compounds were able to pass through the skin mounted between two half-cells of a diffusion well apparatus.

The results show that morphine (0.072% w/v in 250 μl), codeine and hydromorphone have low permeability coefficients (i.e., are poorly absorbed), which corresponds to their lower hydrophobicity and greater lipophilicity. The authors conclude that morphine, as well as other opioids, are not efficiently absorbed through human skin. For example, the authors state on page 831 that, "as a group, these [opioids] appear totally unsuited for transdermal delivery..." As observed by the authors, a topical composition is clinically inadequate due to lack of bioavailability when absorption is delayed to this extent. Thus, the conclusion in Roy *et al.*

teaches the failure of a topical, antinociceptive composition comprising morphine. By contrast, the present invention teaches a pharmaceutical composition comprising morphine and lidocaine, administered topically—such as to the surface of skin—and that synergistically potentiates an antinociceptive response at peripheral sites. Just like Moore *et al.*, Roy *et al.* teach away from a topical, antinociceptive composition comprising opioid analgesics, including morphine.

In addition, Roy *et al.* (J. Pharm. Sciences 83:1723-1726; 1994) describe a study in which the permeability of morphine to skin was further evaluated. The results showed that morphine (4% w/v in 250µl) was relatively impermeable to skin, as determined by both a human cadaver skin model and a mouse skin model. For example, the authors stated on page 1724 that the permeability coefficients of other drugs studied are "several orders of magnitude higher than those found for morphine hydrochloride..." In other words, the bioavailability of topical morphine was much lower than that of the other drugs in the study.[1] This finding also teaches away from a topical, antinociceptive composition comprising morphine.

Not only was the use of compositions comprising topical morphine discouraged by prior teaching in the art, the use of compositions comprising topical lidocaine is discouraged as well. At least one medical report teaches that use of lidocaine as a topical composition provides insufficient effect, an additional finding that teaches away from the present invention:

Leopold *et al.* (J. Invest. Dermatol. 113:304-307; 1999) describe a study evaluating the time course of the pharmacodynamic response of cutaneously (i.e., topically) applied local anesthetic bases. A total of eight volunteers received each of six local anesthetics, including lidocaine, at a concentration of 100 mg per ml (10% w/v concentration), 7 days apart. The anesthetics were applied to the forearm of each volunteer, within an area of 3.5 x 3.5 cm^2. To assess the anesthetic response, thermal threshold measurements were taken over time using a thermal sensory analyzer. Both cold and warm sensations were tested, as well as, cold and heat pain thresholds. Further, the forearm was challenged with a needle insertion.

Although the authors claimed that the results characterize lidocaine as one of the most efficient local anesthetics, both with respect to thermal threshold test results and to needle insertion challenge, the results are not clinically significant. The maximum anesthetic effect is

[1] The results further showed that upon stripping with Scotch tape to effectively remove the entire stratum corneum of the human cadaver skin and the hairless mouse skin, permeation of the drugs increased. Stripping of the stratum corneum was undertaken only to determine how the outer skin layer contributed to the permeability of the drugs, and

reached after 2-3 hours however, it is generally recognized in the art that the anesthetic effect needs to take affect in substantially less time to be clinically useful. Thus, in this regard, Leopold *et al.* teaches away from the use of topical, antinociceptive compositions comprising lidocaine.

In summary, the references discussed above teach away from the claimed use of topical compositions in at least two ways:

- Reporting insufficient effect of peripherally-acting morphine
- Reporting insufficient effect of topical morphine or lidocaine

III. Combining the Cited References Fails to Result in the Claimed Use

The combination of the cited references fails to overcome the prior presumption in the art regarding the lack of effect of morphine or lidocaine at peripheral sites.

Saito *et al.*, as acknowledged by the Examiner on page 3 of the Office Action, fails to disclose the use of a topical composition comprising both morphine and lidocaine. Saito *et al.* exhibits intrathecal administration of morphine and lidocaine to provide a systemic effect. As discussed above, systemic administration cannot be equated with topical administration. In view of the discouraging results published in the prior art (discussed above), one skilled in the art would distinguish the systemic methods in Saito away from the claimed methods, finding no teaching or suggestion of peripheral use therein. Indeed, Saito is silent as to any form of peripheral use.

Similarly, the Stein patent fails to teach or suggest the present invention. The Stein patent requires use of hyperosmolar solutions of opioids or anesthetics (or mixes thereof) such that the drugs first pass into non-inflamed tissue in order to reach inflamed tissue. The effect is therefore downstream from the site of administration.

Importantly, the Stein patent does not teach or suggest that there is a synergistic effect between opioid analgesics and local anesthetics at peripheral sites, which is the unexpected result of the instant invention. In fact, the Stein patent does not teach that use of two agents in combination would be any better than the use of a single agent alone, much less synergistic. Stein instead attempts to solve the problems of the prior art through use of a hyperosmolar solution. This marks a clear distinction between the Stein patent and the instant invention.

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thus, was not meant to test a clinically relevant feature of permeability of the drugs since effective topical treatment would not require a first removal of the stratum corneum.

Although the Office believes that Stein may suggest topical administration of the hyperosmolar solution, the suggestion, if any, is not motivating. None of the experimental data shows the Stein compositions to be efficacious when topically applied. In fact, all of Stein's results were obtained by injection of the analgesic. The patent offers no empirical evidence that topical administration of a single agent, much less a combination of agents, would be effective, and thus the expectation of success is not met.

Taken either alone or together, the cited references do not overcome the prior teaching in the art with regard to the lack of effect that resulted from the use of topical compositions comprising morphine or lidocaine and at peripheral sites.

Even more, the combination of Saito with Stein falls short of teaching the claimed methods or suggesting the need therefor. Saito teaches that systemic lidocaine and morphine are synergestic. Stein proposes that lidocaine and morphine are effective—but not synergistic—in a topical hyperosmolar solution. The combination of Saito with Stein does not teach or suggest a combination that is synergistically effective at peripheral sites, or effective at all in the absence of a hyperosmolar solution.

On page 4 of the Office Action, the Examiner states:

> In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. synergistic potentiation between the peripheral pathways that mediate antinociceptive responses) are not recited in the rejected claim(s).

Applicants respectfully traverse this rejection. The claims recite topical administration of a pharmaceutical composition "in an amount and duration sufficient to potentiate an antinociceptive response." According to Merriam Webster's Collegiate Dictionary, Tenth Ed., the definition of potentiate, as it relates to this usage, is "to augment the activity of (as a drug) synergistically." The claims therefore do include the feature of synergistic mediation of an antinociceptive response. To clarify the scope of the claims, the amended claims now recite that the synergistic effect occurs at peripheral sites.

In summary, there is no teaching or suggestion for the claimed methods in view of their unexpected success and the teaching away in the art. It is respectfully submitted that the claimed methods are non-obvious. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 is requested.

CONCLUSION

Applicants believe that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

If any issue remains as an impediment to allowance, a further interview with the Examiner and her SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

11. (Amended) A method of providing topical analgesia to a subject comprising topical administration of a pharmaceutical composition comprising morphine, lidocaine and[at least two compounds, one effecting opioid analgesia and one effecting local anesthesia, wherein the pharmaceutical composition is administered in] a physiologically acceptable topical excipient [and] in an amount and a duration sufficient to potentiate a synergistic antinociceptive response at peripheral sites.

16. (Amended) The method according to claim 11, wherein the morphine[analgesic] is administered in a dose of about 0.01% to about 25%.

17. (Amended) The method according to claim 11, wherein the morphine[analgesic] is administered in a dose of about 0.1% to about 10%.

18. (Amended) The method according to claim 11, wherein the morphine[analgesic] is administered in a dose of about 0.5% to about 5%.

19. (Amended) The method according to claim 11, wherein the morphine[analgesic] is administered in a dose of about 0.01% to about 1%.

20. (Amended) The method according to claim 11, wherein the morphine[analgesic] is administered in a dose of about 0.01% to about 0.05%.

22. (Amended) The method according to claim 11, wherein the lidocaine[local anesthetic] is administered in a dose of about 0.01% to about 25%.

23. (Amended) The method according to claim 11, wherein the lidocaine[local anesthetic] is administered in a dose of about 0.1% to about 15%.

24. (Amended) The method according to claim 11, wherein the lidocaine[local anesthetic] is administered in a dose of about 0.5% to about 5%.

25. (Amended) The method according to claim 11, wherein the lidocaine[local anesthetic] is administered in a dose of about 0.01% to about 1%.

26. (Amended) The method according to claim 11, wherein the lidocaine[local anesthetic] is administered in a dose of about 0.01% to about 0.05%.